

Androgens and Skeletal Muscle

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Introduction

Tremendous scientific interest has been devoted in recent years to the role of androgens (particularly testosterone) in skeletal muscle, primarily in hypogonadal and elderly populations. Reports of the anabolic effects of androgens emerged in part from anecdotal accounts of athletes who reported gains in muscle strength and mass following androgen administration. These reports have helped to spur much research into both the mechanisms of these effects and the potential therapeutic value of androgen supplementation. It is well established that aging diminishes muscle strength and size, contributing to a number of serious health problems such as increased risk of falls and fractures and decreased mobility [1, 2]. In males it has been repeatedly demonstrated that a decline in gonadal function occurs after the fifth decade, and although this decline in testosterone levels is often sub-clinical, several manifestations of such age-related hypogonadism, or andropause, can present serious health problems for affected

individuals. Some associated conditions include sarcopenia, decreased thermoregulatory function, increased adiposity, increased bone resorption (e.g. leading to increased frailty and risk of fall-related injury), increased insulin resistance, decreased basal metabolic rate, impaired lipid metabolism, decreased sexual drive and depression.

The potential health problems linked to andropause and the associated health care costs make androgen supplementation an attractive option for the treatment of this condition. Since the mechanism of testosterone's action on skeletal muscle is still poorly characterized and appears to be part of a multi-factorial system of functional regulation, the appropriate therapeutic dosage has yet to be firmly agreed upon [3-5]. Exogenous testosterone administration also has many potential side effects, particularly at supraphysiologic levels, and safety is thus a concern for determining appropriate pharmacologic dosing.

In this review we examine some of the current research surrounding androgens and skeletal muscle, particularly with regard to aging and muscle function.

Androgens and Aging

It has been estimated that 50% of men over the age of 50 are hypogonadal, although the deficiency is often sub-clinical [6, 7]. This age-related decline in gonadal function has been termed andropause, but unlike menopause, the condition does not present in all men, and the symptomology and pathophysiology vary considerably [8, 9]. Clinical symptoms of andropause include decreased muscle mass and strength, depressed mood, decreased libido, increased adiposity and osteoporosis [8, 9]. Prostatic gland hypertrophy and gynecomastia are also frequently associated with andropause. Decreased serum testosterone is characteristic of this condition, and depression in serum testosterone can be seen as early as the fifth decade [10]. Additionally,

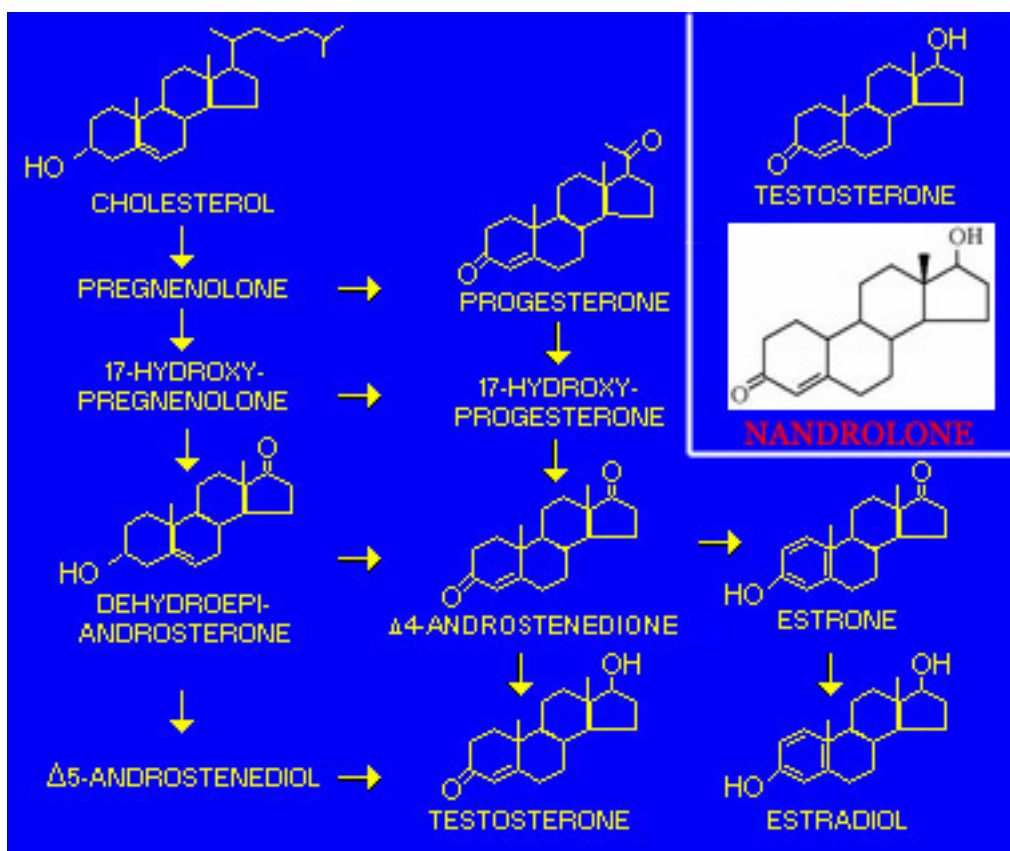
sex-hormone binding globulins (SHBG) levels increase in aging men [11, 12], and the levels of bioavailable testosterone decline [13]. Though it is clear that testosterone is important in the regulation of skeletal muscle function, the clinical implications of this decline in gonadal function are not completely understood. However, the decline in physical function that is associated with the andropause appears to be related to the role that testosterone plays in regulating muscle growth. Mauras et al. induced hypogonadal states in young men [14] using a gonadotropin releasing hormone (GRh) analog and found decreases in strength, fat oxidation and increases in protein breakdown and adipose tissue. These findings mirror the effects of the decline in gonadal function found in aging men, and support the role of testosterone in the effects of age-related sarcopenia and metabolic alteration.

Similar declines in skeletal muscle mass and strength occur in muscle-wasting conditions secondary to AIDS and trauma, associated with decreased levels of serum androgens [15-17]. In such populations androgen therapy is clinically justified as a means of increasing muscle protein synthesis, muscle strength and mass [18]. In elderly populations suffering from age-related sarcopenia secondary to andropause, testosterone therapy can be beneficial in increasing or maintaining muscle strength and size [12]. Elderly men suffering from hypogonadism have shown decreases in muscle protein breakdown [19], muscle protein synthesis [20], lean body mass [19, 21, 22], and muscle strength. However, the increases in muscle strength associated with testosterone supplementation have been found to be disproportionate to increases in muscle mass [21-23], indicating a need for more data specifically outlining the benefits of testosterone administration in elderly populations. Although the decline in muscle strength is often more pronounced than the decline in muscle mass, muscle strength correlates with muscle size. Accordingly, Frontera et al. showed in a 12-year longitudinal study that reduced cross-sectional area of muscle was a major factor in the decline in muscle strength

associated with aging [24]. During aging, the decline in muscle strength is often disproportionate with the decline in muscle mass, suggesting perhaps that additional factors contribute to strength loss in the elderly. Since it has been shown that testosterone administration alone does not improve the specific tension of skeletal muscle, and that resistance exercise is necessary to alter contractile function [5], a combination of supplementation and strength training is likely to be most effective interventional strategy for improving muscle function in older individuals.

Androgens and Protein Balance

It is well-established that administration of both testosterone and its synthetic analog oxandrolone is capable of inducing skeletal muscle growth in both

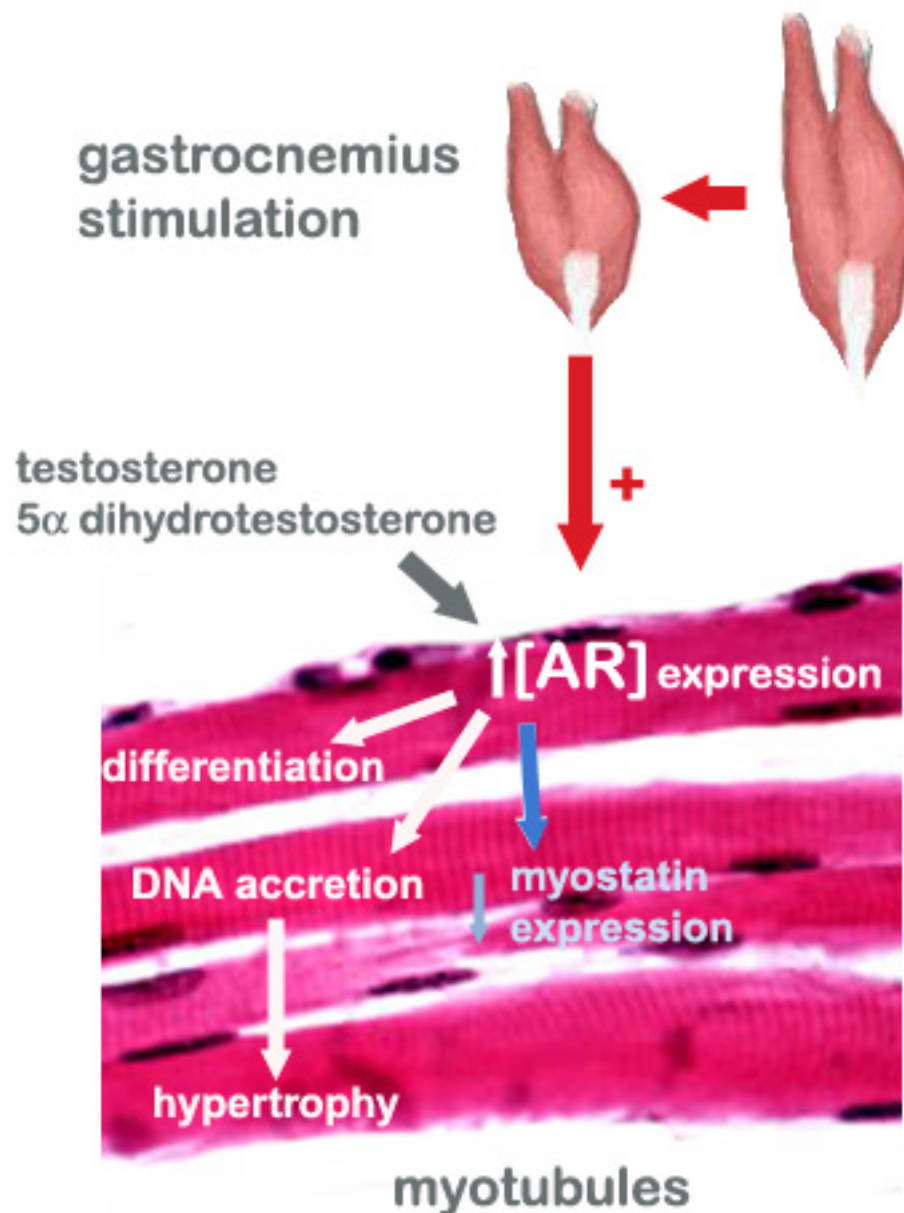


hypogonadal [12, 25] and eugonadal individuals [19]. This effect can be induced in both young [3, 5, 26-28] and elderly men [5]. The mechanism of this net myotropic effect appears to differ in these groups however. In the young, we demonstrated an increase in the fractional synthetic rate (FSR) of skeletal muscle protein, indicating an increase in net protein synthesis following 5-days of oxandrolone

administration [27]. Conversely in the elderly we observed a decrease in net protein breakdown following administration of amino acids and oxandrolone [29]. Though muscle quality (the ratio of muscle mass to strength) has been shown to improve only with the addition of resistance training [28], it is promising that pharmacological and nutritional intervention alone is sufficient to reverse catabolism in older men.

There have been several studies evaluating the efficacy of various methods for exogenous androgen administration [21, 30-34] as well as different dosages, although the debate is ongoing. Since testosterone administration has been associated with numerous virilizing side effects (e.g. hirsutism, acne, hair loss) as well as behavioral alterations, the determination of appropriate clinical regimens for testosterone administration is crucial. The potential negative effects of long-term androgen administration vary and are poorly understood [3], and thus more data is needed regarding long-term androgen supplementation. Currently, clinical use of androgens is limited to hypogonadal populations, but with continued research into their use in other androgen-deficient populations, viable treatment paradigms can be established in populations such as elderly men to counteract increases in muscle protein breakdown.

Molecular Mechanism of Androgens and Skeletal Muscle



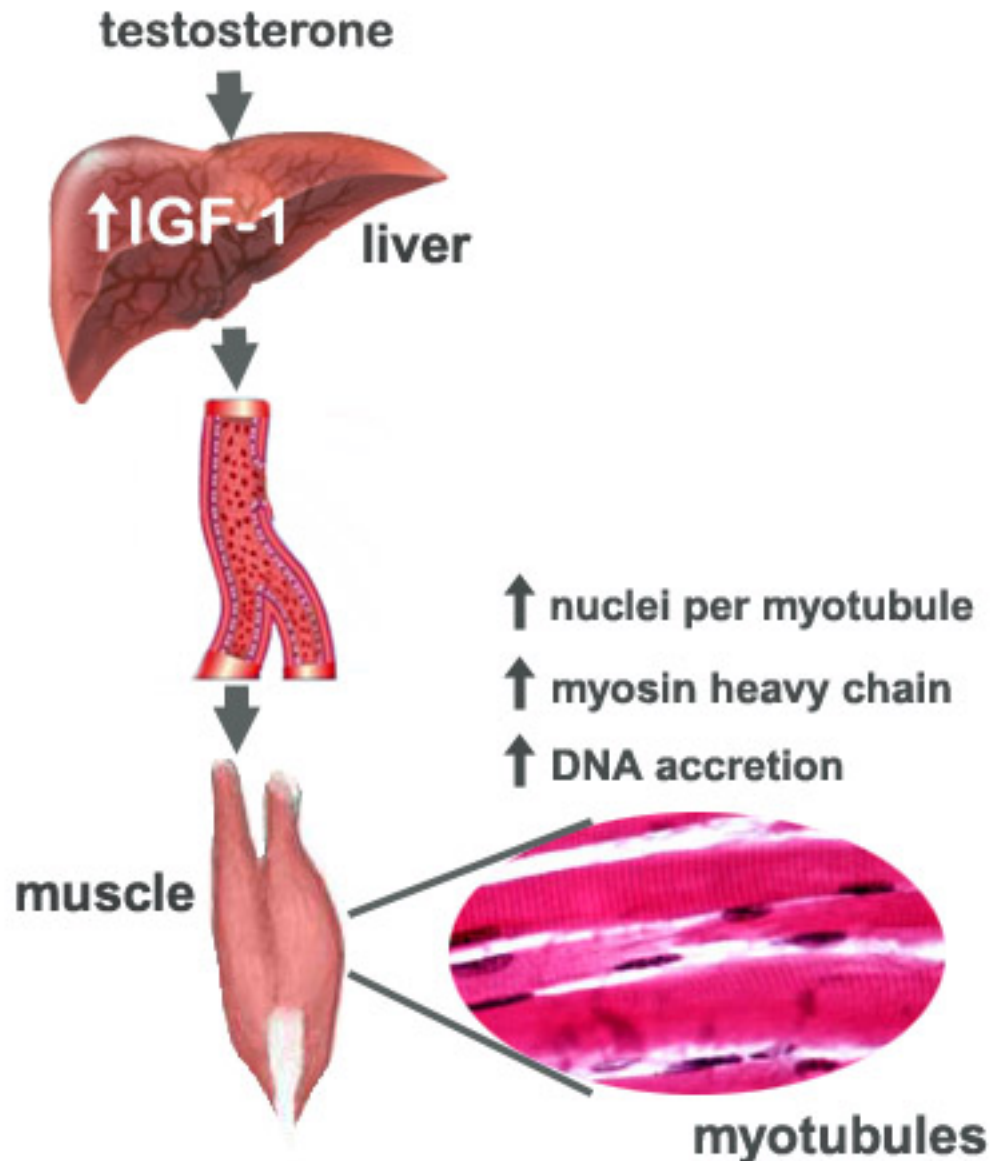
The molecular mechanisms underlying the anabolic effects of androgens on skeletal muscle are poorly understood. It is well known that androgens mediate their effects, both directly and indirectly, via the androgen receptor (AR), the gene for which is located on the

X-chromosome. The direct effect of testosterone in skeletal muscle results from the ability of both testosterone and its metabolite, 5-[alpha]-dihydrotestosterone to agonize the AR, specifically in satellite cells and myonuclei [35]. Inoue et al have shown that AR levels are upregulated following gastrocnemius stimulation in rats, supporting the role of AR activity in skeletal muscle hypertrophy [25]. The primary effect of this receptor interaction appears to involve mesenchymal differentiation [35] and DNA accumulation within the myocyte [18]. It is known that DNA accretion is necessary for skeletal

muscle hypertrophy [27], though the mechanism by which AR activity affects DNA accumulation is not currently understood.

The indirect action of testosterone on skeletal muscle appears to involve both the modulation of transcription factors within the myocyte and the induction of endocrine and paracrine factors in other tissues [18]. For instance, testosterone has been shown to indirectly induce skeletal muscle growth by upregulating levels of hepatically-derived insulin-like growth factor (IGF-I [36]). Increased serum levels of IGF-I have been correlated with an increase in myosin heavy chain content and mean number of nuclei per myotubule [37], suggesting that IGF-I is at least partly involved in the DNA accretion known to be necessary for skeletal muscle hypertrophy, as well as inducing an anabolic effect in myocytes [19].

Androgens may also exert an indirect effect on skeletal muscle function by counteracting the actions of glucocorticoids. For instance, following trauma glucocorticoid levels rise and a net breakdown of skeletal muscle is induced.



Testosterone has been shown to have a high affinity for the glucocorticoid receptor [38], and once bound seems to be capable of antagonizing the catabolic effects of glucocorticoids. This antagonism is observed with both exogenous [39] and endogenous glucocorticoid effects. We have demonstrated increased protein synthesis in young men following an overnight fast with oxandrolone administration, indicating that the normal catabolic glucocorticoid response to fasting may be opposed by androgen binding [27].

In addition to the effects of testosterone on differentiation and DNA

accretion, androgens appear to regulate skeletal muscle function via altering myostatin expression in myocytes. Myostatin is a member of the TGF-beta superfamily of secreted growth factors which are involved in the negative regulation of skeletal muscle mass [40]. Myostatin levels are elevated in sarcopenic populations, and transgenic mice lacking the myostatin-encoding gene show markedly increased muscle size. Additionally, following resistance exercise myostatin levels fall [41], suggesting that myostatin is an important regulator of skeletal muscle function, and that pharmacological antagonists could be of potential therapeutic value in the treatment of age-induced sarcopenia.

Conclusions

The decline in physical function associated with aging can drastically diminish the quality of life of elders, as well as presenting a persistent and costly problem for the medical community. The loss of muscle mass that occurs with aging is well-documented, and is a major factor in the associated metabolic and functional alterations in this population. Our current understanding of androgens and skeletal muscle lends promise to the potential treatment of age-related sarcopenia via androgen supplementation, but much data is still needed linking the mechanisms of hypogonadism, aging and muscle function. Additionally, large prospective clinical trials are required for elucidating the long-term effects of androgen therapy and for clarifying the most efficacious dosage and timing for the treatment of individuals affected by sarcopenia.

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